REMARKS

Claims 20, 21, and 38-56 are pending in this application. Claims 20, 21, 38-41, and 56 have been withdrawn, and claims 42-55 have been rejected. Independent claim 42 has been amended to clarify that, with respect to the isolated, individual cells receiving a transposon insertion site, the claimed methods comprise sequencing these transposon insertion sites. Support is found on page 47, lines 1-9.

The claim amendments add no new matter.

Prior Rejections

Applicants appreciate the indication on page 2 of the Office Action that the prior rejections based on indefiniteness have been withdrawn.

Rejection under 35 U.S.C. § 103(a)

The Office Action maintains the rejection of claims 42-55 as obvious under 35 U.S.C. § 103(a) over the combination of Charles *et al.* (WO 01/07651; "Charles") and Haselbeck *et al.* (WO 01/70955; "Haselbeck"). Applicants respectfully traverse.

Amended claim 42 and its dependent claims 43, 44, and 47-55 are all directed to a method for identifying a library of putative essential or important genes using a High Throughput Transposon Insertion (HTTIM) database. According to the claimed methods, following mutagenizing a *Staphylococcus* genome, individual cells having at least one transposon insertion site are isolated. The methods comprise

> "sequencing said at least one transposon insertion site in each individual cell to form a database of the polynucleotide sequences of transposon insertion sites, or an HTTIM database."

For example, according to an embodiment of Applicants' claimed method, "Precise transposon insertion sites are determined by an anchored, semi-random PCR method…The PCR product is

then sequenced and the insertion site is entered into an Oracle database for analysis." Specification, page 47, lines 1-8.

As page 5 of the Office Action recognizes, Charles does not suggest *sequencing* transposon insertion sites, but instead *hybridizes* consensus probes of a library which flank inserted transposon sites. With respect to this Transposon Mediated Differential Hybridization (TMDH) method described in Charles, Applicants have recognized that

> ...the problem with this methodology is that it has a high propensity to lead to false positives, and many essential genes will be missed. Furthermore, the method does not yield any detailed information regarding the loci disrupted by transposons, or whether they were hit more than once.
>
> Specification, page 7, lines 18-21.

Charles does not sequence transposon insertion sites; nor does Charles even more generally suggest any benefit in doing so. Nevertheless, it is the Office's position that such a modification of Charles' hybridization method would have been obvious due to time and cost savings. Office Action, paragraph bridging pages 5-6. However, no support for this assertion is cited in Charles or elsewhere.

Insofar as the Office is attempting to officially notice a fact, this is respectfully traversed. Official Notice is only permissible for those few facts that are of a "notorious character" and that are "capable of instant and unquestionable demonstration". M.P.E.P. § 2144.03(A). It is improper to use Official Notice for conclusions of law, and particularly as the principal evidence upon which a rejection was based. *Id.* The Office is expressly required to provide specific factual findings predicated on sound technical and scientific reasoning to support taking Official Notice. M.P.E.P. § 2144.03 (B). The M.P.E.P. goes on to explain that this means that the Office

should present Applicants with the explicit basis on which Official Notice is based so that Applicants are able to challenge the assertion in the next reply after the Office Action.

The Office Action additionally cites the teachings on pages 94-96 of Haselbeck for the proposition that comparing nucleotide sequences to a known genomic sequence would have been obvious. Haselbeck, however, does not sequence transposon insertion sites, or even suggest random transposon insertion at all. Haselbeck is instead directed to a fundamentally different method, involving the *direct* identification of nucleic acid fragments that impact cell growth. According to Haselbeck's method, these fragments are inserted on a vector, downstream of an inducible promoter and then expressed in a test population of cells. Haselbeck, page 66, lines 2-34. The sequences of interest, in terms of their ability to negatively impact cell growth, are then analyzed to directly determine their sources, or genomic regions. Haselbeck, page 67, lines 7-12.

Charles, in contrast, is concerned with the *indirect* identification of essential genes, by first generating consensus probes from polynucleotide sequences of non-essential genes flanking transposons. Charles, page 9, lines 13-19. Hybridization experimentation is then performed, and locations of no hybridization, on a gridded array of the genome, are taught to likely correspond to essential genes. Charles, page 13, line 27 to page 14, line 18. In this manner, Charles identifies essential genes indirectly by the process of elimination.

Charles additionally offers specific reasons, emphasizing the importance, in this indirect detection method, of using hybridization experiments in the form of a gridded array:

> The advantage of using a gridded arrays is that a whole genome may be analyzed in one experiment, very quickly and the clones to which the consensus probe does not hybridize are immediately available in a purified form. Additionally, in the case of an organism whose entire genome has been sequenced , for example *E. coli* or *S. cerevisiae*, the order of all open reading frames in the genome is known. Therefore, the order of all the open reading frames represented on a gridded array is known.
>
> Charles, page 14, lines 5-11.

Unlike Charles, Haselbeck directly determines which of a *relatively small number* of nucleic acid fragments have the ability to negatively impact cell growth. This method would not have led one skilled in the art to *sequence* transposon insertion sites, corresponding a *far greater number* of non-essential nucleic acid fragments, in a method for the indirect determination of essential genes involving hybridization. The skilled biochemist would have immediately appreciated, from the disclosures of Charles and Haselbeck, the significantly greater sequencing requirements if Charles were to be modified as proposed in the Office Action. For example, in the case of *S. aureas*, the inventors of the presently claimed methods have generated over 7400 transposon mutants (corresponding to non-essential genes) to provide a database of only 500 to 1500 open reading frames for which no transposon insertions are obtained (corresponding to essential genes). Compared to Haselbeck's methods involving sequencing only the essential genes, one skilled in the art would recognize that modifying Charles to include sequencing of the non-essential genes rather than simply hybridizing consensus probes, would increase the requirement for sequencing by *about 5-fold to 15-fold, with no apparent advantage*. Again, it is only Applicants, not Charles or Haselbeck, who teach the advantages of sequencing of transposon insertion cites over Transposon Mediated Differential Hybridization. In particular, the claimed methods reduce false positives and provide valuable and detailed information regarding the transposon insertion sites. Specification, page 7, lines 18-21.

It is black letter law that obviousness requires at least a suggestion of all of the features in a claim. See *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003). Moreover, according to Supreme Court and Federal Circuit precedent, the obviousness analysis requires "some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." Teleflex Inc. v. KSR Int'l Co., 82 USPQ 1385, 1396 (2007)

(quoting In re Kahn, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)). In reversing rejections based on obviousness, the Board of Patent Appeals and Interferences has clarified that

> The U.S. Supreme Court recently held that rigid and mandatory application of the "teaching-suggestion-motivation," or TSM, test is incompatible with its precedents. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007). The Court did not, however, discard the TSM test completely; it noted that its precedents show that an invention "composed of several elements **is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art**." *Id.*
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> Ex Parte Whalen II, Appeal 2007-4423, July 23, 2008 (emphasis added).

Neither Charles taken alone, nor Charles taken in combination with Haselbeck, meets these legal standards for obviousness. In particular, Charles does not suggest at least the feature of sequencing transposon insertion sites, as claimed. Moreover, there would have been no reason for one to combine Charles with Haselbeck in the manner proposed in the Office Action, for the reasons stated above.

Please withdraw the rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the above amendments remarks, all pending claims of this application are believed to be in condition for allowance. Acknowledgement of the same is respectfully requested. This response is believed to completely address all of the substantive issues raised in the Office Action dated August 31, 2010.

Respectfully submitted,

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